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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,430	03/18/2002	Lorena Muggetti		1505

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EXAMINER	
KHARE, DEVESH	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/070,430	Applicant(s) MUGGETTI ET AL.	
	Examiner Devesh Khare	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-11,13-16,18-20 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-11,13-16,18-20 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09-29-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's Amendment and remarks filed on 09/29/03 are acknowledged.

Claims 7, 12, 17, and 21-24 have been cancelled. Claims 2-6, 8-11, 13, 15, 16 and 18-20 have been amended. New claims 25-27 have been added.

Claims 1-6, 8-11, 13-16, 18-20 and 25-27 are currently pending in this application.

Objection

In claim 18, line 2, '26' should be replaced by '14'.

Appropriate correction is required.

Provisional "Non-Statutory" Double Patenting Rejection

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 8-11, 13-16, 18-20 and 25-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6,8-12,14-16,18-21,24-27 of co-pending Application No. 10/070,416 ('416) in view of Yoshida et al. (WO 84/02270).

The instant invention is directed to a pharmaceutical formulation and product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, human albumin and a

parenterally acceptable carrier or diluent and a method for treatment of cancer with the said composition.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '416 co-pending application discloses a pharmaceutical formulation and product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, and a parenterally acceptable carrier or diluent and a method for treatment of cancer with the said composition. The '416 co-pending application differs from the applicant's invention that the composition of the '416 co-pending application does not include the albumin.

Yoshida et al. disclose the use of estramustine phosphate in microfine particles as cancer control agent (see page 1, lines 1-13). Yoshida et al. disclose that the protein such as albumin can be converted to microfine particle as carriers (see page 5, lines 12-13). Yoshida et al. also disclose that other cancer control agents such as doxorubin hydrochloride or vinblastine sulfate can be used along with the microfine particles bound to estramustine phosphate (see page 7, lines 15-19). It is noted that Yoshida et al. do not disclose the use of the cyclodextrin in the composition.

It would have been obvious to person having ordinary skill in the art at the time the invention was made, to modify the composition of '416 co-pending application by including the albumin, in view of the recognition in the art, as evidenced by the patent Yoshida et al., that disclose that the protein such as albumin can be converted to microfine particle as carriers.

The examiner notes the instant claims and the '416 co-pending application claims do indeed substantially overlap and this obviousness-type double patenting rejection is necessary to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1-6, 8,9, and 13-16 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Martini et al. (WO 96/09072) in combinations with Stella et al. (U.S. Patent 5,134,127) in view of Yoshida et al. (WO 84/02270) of record.

Claims **1-6, 8,9 and 13-16** are drawn to a pharmaceutical formulation and product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, human albumin and a parenterally acceptable carrier or diluent. Additional claim limitations include the weight ratio of estramustine to sulfoalkyl ether cyclodextrin is from 1:0.5 to 1:5, a single infusion dosage of the estramustine phosphate at least 1300 mg or 950 mg, sulfoalkyl ether cyclodextrin is a straight or branched C1-C6 sulfoalkyl ether cyclodextrin, and estramustine phosphate is in the form of N-methyl glucamine salt or lyophilized form or estramustine phosphate and sulfoalkyl ether cyclodextrin in lyophilized form.

It is noted that claims 14-16 are drawn to a pharmaceutical product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, human albumin, a parenterally acceptable carrier or diluent and one or more chemotherapeutic agents. Additional claim limitations include the sulfoalkyl ether cyclodextrin is sulfoalkyl ether β-cyclodextrin and chemotherapeutic agent is doxorubicin or vinblastine.

Martini et al. teach a composition comprising an estramustine phosphate and a cyclodextrin (see abstract). Martini et al. disclosed the molar ratio between drug (estramustine phosphate) and the cyclodextrin from 1:0.5 to 1:10 (see page 5, lines 17-20) and a pharmaceutical formulation with pharmaceutically acceptable carriers or diluents (see page 6, lines 1-2). Martini et al. also suggest on page 5, lines 4-9, the use of cyclodextrin to permit the passage of the estramustine phosphate in solution and the dosage for oral administration from 50 to 1500 mg (see page 6, lines 4-6). Martini et al. disclosed that the preferred cyclodextrin are β-cyclodextrin (see page 4, line 16). Furthermore, on page 2, lines 1-6, a freeze-dried or lyophilized form of a drug-cyclodextrin complex is suggested. Martini et al. differs from the applicant's invention that Martini et al. do not provide an example of a pharmaceutical composition, comprising the estramustine derivative and a cyclodextrin containing human albumin, however Martini et al. does provide motivation to use estramustine and its disodium salt (page 3, line 15) and a cyclodextrin, for cancer therapy (page 6, lines 9-10). It is noted that Martini et al. does not provide specific disclosures regarding the N-methyl

glucamine salt of estramustine phosphate and specifically the cyclodextrin derivative: sulfoalkyl ether cyclodextrin.

Stella et al. teach a method of using sulfoalkyl ether cyclodextrin derivatives as solubilizing agents for water insoluble drugs for oral, intranasal, or parenteral administration (see abstract). Stella et al. disclose a composition on col. 7,line 39, containing the complex of sulfoalkyl ether cyclodextrin and estradiol. Stella et al. disclosed the straight or branched cyclodextrin derivatives on col. 5, lines 29-39). Stella et al. also disclose a pharmaceutical formulation containing a complex of a drug with cyclodextrin derivative together with a pharmaceutical acceptable carrier and optionally other therapeutic agents (see col. 8, lines 34-39). It is noted that Stella et al. does not provide specific disclosures regarding the use of human albumin in the composition. Yoshida et al. disclose the use of estramustine phosphate in microfine particles as cancer control agent (see page 1, lines 1-13). Yoshida et al. disclose that the protein such as albumin can be converted to microfine particle as carriers (see page 5, lines 12-13). Yoshida et al. also disclose that other cancer control agents such as doxorubin hydrochloride or vinblastine sulfate can be used along with the microfine particles bound to estramustine phosphate (see page 7, lines 15-19). It is noted that Yoshida et al. do not disclose the use of the cyclodextrin in the composition.

Therefore, one of ordinary skill in the art would have found the applicants claimed pharmaceutical formulation and product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, human albumin and a parenterally acceptable carrier or diluent, to have been obvious at the time the invention was made having the above cited

references before him. Since Martini et al. teach a composition comprising an estramustine phosphate and a cyclodextrin, Stella et al. teach a method of using sulfoalkyl ether cyclodextrin derivatives as solubilizing agents for water insoluble drug such as estradiol, and Yoshida et al. disclose the use of estramustine phosphate in microfine particles where albumin can be converted to microfine particle as carriers, one skilled in the art would have a reasonable expectation for success in combining the teachings of these references to accomplish a pharmaceutical formulation or a product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, human albumin and a parenterally acceptable carrier or diluent . The motivation for doing so is provided by Martini et al., which disclose a pharmaceutical composition containing the estramustine derivative and a cyclodextrin, suitable for oral administration of estramustine derivative to a cancer patient.

Claims 10, 11, 18-20 and 25-27 are rejected under 35 U.S.C. 103 (a) as being unpatentable over co-pending Application No. 10/070,416 ('416) in view of Yoshida et al. (WO 84/02270).

The instant invention is directed to a method for treatment of cancer comprising parenterally administering the formulation of claim 1 or claim 14 to a patient. Additional claim limitations include the cancer is prostate cancer, breast cancer, melanoma, lung cancer, pancreatic cancer, colorectal cancer, ovarian cancer or cancer of the brain; and administration is parenterally or intravenous.

The '416 co-pending application teaches a pharmaceutical formulation and product containing estramustine phosphate, a sufoalkyl ether cyclodextrin, and a parenterally

acceptable carrier or diluent and a method for treatment of cancer with the said composition. The '416 co-pending application differs from the applicant's invention that the composition of the '416 co-pending application does not include the albumin. Yoshida et al. disclose the use of estramustine phosphate in microfine particles as cancer control agent (see page 1, lines 1-13). Yoshida et al. disclose that the protein such as albumin can be converted to microfine particle as carriers (see page 5, lines 12-13). Yoshida et al. also disclose that other cancer control agents such as doxorubin hydrochloride or vinblastine sulfate can be used along with the microfine particles bound to estramustine phosphate (see page 7, lines 15-19). It is noted that Yoshida et al. do not disclose the use of the cyclodextrin in the composition.

It would have been obvious to person having ordinary skill in the art at the time the invention was made, to modify the composition of '416 co-pending application by including the albumin, in view of the recognition in the art, as evidenced by the patent Yoshida et al., that disclose that the protein such as albumin can be converted to microfine particle as carriers. The motivation is provided by '416 co-pending application that claims a method for treatment of cancer with the said composition (see claims 10,11,18-20 and 25-27).

Rejection Maintained

Rejection of claims **1-6, 8,9, and 13-16** under 35 U.S.C. 103(a), is maintained for the reasons of record.

The amended and new claims **10, 11, 18-20 and 25-27** are rejected under 35 U.S.C. 103 (a) as being unpatentable over co-pending Application No. 10/070,416 ('416) in view of Yoshida et al. (WO 84/02270) (see the rejection of record).

Response to Arguments

Applicant's arguments filed on 09/29/03 traversing the rejection of claims **1-6, 8,9, and 13-16** under 35 U.S.C. 103(a), have been fully considered but they are not persuasive.

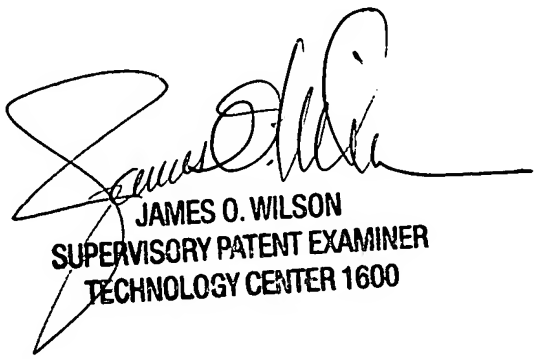
Applicants argue that "Martini does not teach or suggest parenteral formulations of estramustine phosphate" and "Stella teaches that sulfoalkyl ether cyclodextrin derivatives are useful as solubilizing agents for water insoluble drugs" & "Estramustine phosphate is water soluble". It is noted that estramustine phosphate is water soluble, but the applicants also disclose that estramustine derivatives are insoluble in the gastrointestinal tract due to contact with cations (page 3, line 23 through page 4, line 5). Martini et al. does not disclose the parenteral formulations of estramustine but discloses that the precipitate of estramustine with a cation can be solubilize with cyclodextrins (page 14, lines 10-14); and Stella et al. teach a method of using sulfoalkyl ether cyclodextrin derivatives as solubilizing agents for water insoluble drugs for oral, intranasal, or parenteral administration (see abstract, col. 8, lines 47-51), which are rendered obvious by the disclosure.

2. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (703)605-1199. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Supervisory Patent Examiner, Art Unit 1623 can be reached at 703-308-4624. The official fax phone numbers for the organization where this application or proceeding is assigned is (703) 308-4556 or 308-4242.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



Devesh Khare, Ph.D.,JD(3Y).
Art Unit 1623
February 11,2004